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(54) Title: PARENTERAL PHARMACEUTICAL COMPOSITIONS CONTAINING AMMONIUMALKYL SALTS OF 2-ARYLPROPIONIC ACIDS

(57) Abstract

A pharmaceutical composition for parenteral administration having anti-inflammatory and analgesic properties which contain, as active principle, alkylammonium salts of 2-arylpropionic acids.

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Description

Parenteral pharmaceutical compositions containing ammoniumalkyl salts of 2-arylpropionic acids.

The object of the present invention consists of pharmaceutical compositions suitable for parenteral administration which contain alkylammonium salts of 2-arylpropionic acids.

In particular, although the parenteral pharmaceutical compositions of the invention are suitable to be obtained with any 2-arylpropionic acid having antiinflammatory activity, they preferably contain, as 2-arylpropionic acid, ketoprofen or 3-benzoyl-α-methylbenzeneacetic acid, ibuprofen or 2-(4-isobutylphenyl)propionic acid, naproxen or (S)-6-methoxy-α-methyl-naphthaleneacetic acid and tiaprofenic acid or 5-benzoyl-α-methyl-2-thiopheneacetic acid, the ketoprofen being the 2-arylpropionic acid particularly preferred.

One of the advantages represented by the pharmaceutical compositions of the invention is that it allows for the administration of the non-steroid antiinflammatory substance by a route of administration, the parenteral one, which does not show side effects as shown by the pharmaceutical forms administered by topical route such as, for example, creams, lotions, gels or ointments which, because of their easy methods of application, are widely used. It is in fact known from literature on the subject that topical administration of non-steroid anti-inflammatory drugs can, in a more or less serious manner, provoke damage to the patient's skin due to

the fotolability of the drug which, in the presence of light, undergoes a degradation process, the products of which interfere negatively on the cellular membrane by the formation of free radicals.

The pharmaceutical compositions of the invention represent, moreover, a notable improvement as far as stability and convenience of use and safety are concerned with respect to the compositions already on the market containing the same anti-inflammatory drugs.

A decisively more advantageous aspect of said pharmaceutical compositions is that their administration causes uneasiness but tolerable, with respect to the pain, sometimes intense, caused by the compositions for parenteral use on the market containing the same anti-inflammatory drugs.

In particular, as far as ketoprofen is concerned, the relative smallness of the side effects and the recognised effectiveness in the symptomatic treatment of rheumatoid arthritis, in osteoarthritis, in anchylosing spondylitis, of acute painful articular and periarticular symptoms of the musculoskeletal system, in gout and in dysmenorrhea, in the treatment of pain and inflammation which accompanies or follows orthopaedic operations, have made of such a drug one of the active principles of largest use in oral administration among anti-inflammatory non-steroid drugs of current therapeutical use.

The analgesic and anti-inflammatory effect of ketoprofen has been, in large measure, correlated to its capacity, or more specifically, to the capacity of

its S-enantiomer, of inhibiting the prostaglandin synthesis. More recently, it has been recognised that the R-enantiomer, which in human beings does not undergo an appreciable metabolic conversion in the S-antipode, has its own analgesic property, mediated by mechanism of action which, even though not fully clarified, seem to be completely independent from the prostaglandin synthesis block.

Pharmaceutical formulations for parenteral use containing as active principle ketoprofen and/or its enantiomers are thought to be particularly useful in the treatment of acute exacerbations of painful manifestations and as adjuvant in the symptomatic therapy of pain in persons suffering from terminal cancer, in individual therapeutic treatment as in association with muscle relaxants, pain-killers and central analgesics.

The 2-arylpropionic acids with anti-inflammatory activity of the present invention are made up of highly lipophilic carboxylic acids and as such are scarcely soluble in water. Nonetheless it is possible to prepare solutions of said acids, after salification in aqueous vehicles containing a surplus of a hydrate, of a bicarbonate and/or of an alkaline carbonate or an earth alkaline carbonate such as, for example, sodium hydroxide, sodium bicarbonate, of a preferably basic

α-aminoacid or of a hydroxyalkylamine, eventually in the presence of preservatives and excipients and/or dispersing agents.

Said solutions of the 2-arylpropionic acids present a

gradual instability easily evidenced from a progressive yellowing, sometimes followed by turbidity and by separation of floccules, phenomena which become more noticeable with the temperature's increase and after the solution's prolonged exposure to the light. To overcome said difficulty recourse was made to lyophilized pharmaceutical formulations from which the injectable solution is reconstituted just at the moment of use by means of solubilization in the proper solvent. These solutions contain, furthermore, variable quantities of preserving substances among which are mainly used the p-hydroxybenzoate of methyl and propyl, and supporting materials in excess such as, for example, glycine, to ensure the volume and compactness of the lyophilized substance itself. The use, together with the active principles, of a ponderal excess of supporting materials imply that the constituted solutions present pH values which vary from 6.5 to 7.3 and definitely result hypertonic. In fact, osmolarity values are measured covering an interval from 650 to 1150 mOsm/kg, which are not very compatible with the isotonicity of biological fluids which present values comprised between 275 and 295 mOsm/kg. As a result, the administration of such solutions causes pain to the patient and moreover superficial liquid effusions can come about. The presence of remarkable quantities of excipients and of the preserving agents in the solution can moreover be the cause of risks deriving from the patient's individual susceptibility to said substances.

It is known that, on the English market, formulations

have long been introduced for the extemporary use consisting of a ketoprofen solution in a mainly aqueous medium containing an excess of l-arginine, benzylic alcohol and citric acid; said solutions, which present a global pH of about 6.7 are supplied in dark glass containers for a better control of their stability.

The pharmaceutical compositions suitable for parenteral use object of the present invention, are made up of aqueous solutions of alkylammonium salt of 2-arylpropionic acids chosen from the group consisting of ketoprofen, ibuprofen, naproxen and tiaprofenic acid in racemic or in enantiomeric form, which present osmolarity values comprised in the range 270-310 mOsm/kg and pH values comprised in the range 7.0-7.5.

As alkylammonium bases are utilised bases which include alkyl radicals eventually substituted with hydroxy radicals: in the case that the alkylammonium base exists in a racemic or enantiomeric form, the salts can comprise either one or the other of said forms. Bases particularly preferred are α-aminoacids such as lysine and particularly preferred is the salt formed with the forms of said aminoacid having the natural configuration. Another preferred base is the dropropizine or 3-(4-phenyl-1-piperazinyl)-1,2-propanediols. The salifying acid is preferably employed in its racemic form even though salts formed from its separate enantiomers are comprised within the scope of the invention.

The particularly preferred salts are those of (R,S)-ketoprofen with d,l-lysine and with l-lysine

respectively described in US 4,279,926 (21.07.81) and BE 882.889 (14.05.80). Other salts, as for example the R- or S-ketoprofen salts with the separated stereoisomers of lysine and dropropizine, are also known and have been described in WO 94/20449 (15.09.94).

According to the process of the invention, the pharmaceutical compositions suitable for parenteral use containing salts of a 2-arylpropionic acid selected from the group consisting of ketoprofen, ibuprofen, naproxen and tiaprofenic acid with alkylammonium bases are prepared by solubilizing in an inert-gas atmosphere and away from light, in an aqueous solution, at a pH ranging from 7.0 and 7.5, the alkylammonium salt of the chosen 2-arylpropionic acid.

The use of an inert gas during the preparation of the solutions and their subsequent conservation allows the reaching of such a degree of stability so as to avoid a recourse to the use of preservatives and co-solvents such as, for example, alcohols or glycols for preventing the progressive yellowing of the solutions. Inert gases particularly preferred are those which are chemically inert with solvents and solutes and are compatible with the foreseen pharmaceutical use: these are, as example, nitrogen and the rare gases helium and argon and their mixtures.

Besides to grant the composition of the invention a good tolerability, the lack of benzyl alcohol or other solvent, except water for injectable preparations, also gives the consumer a precise information about

the quality of the composition itself. In fact, should the pharmaceutical composition undergo alterations due to an incorrect storage, the appearing of a characteristic whitish opalescence indicates these alterations immediately and therefore the pharmaceutical composition will be not administered.

The appearance of said opalescence representing a very sensitive index of the pharmaceutical quality of the active principle contained in the composition of the invention, is a guarantee of the quality of the composition and furthermore it represents a noticeable improvement in respect to those compositions which contain co-solvent agents, such as in particular benzyl alcohol, and consequently do not make evident the possible presence of alterations which would cause the pharmaceutical quality of the composition not anymore acceptable.

The packaging, in suitable containers of dark glass optionally disposed in a box wherein each container is separately packaged, as well as the other characteristic of the composition of the invention assures a full stability to the product as demonstrated by the tests carried out.

Moreover it has been observed that the pH adjustment of the injectable solution between 7.0 and 7.5, allows for the bringing about of, not only a useful increment of osmolarity towards that degree of hyperosmosis which better than

a slight hypo-osmosis adapts itself to a good tolerability of the injectable solution, but also an ulterior increment in the stability of the darkening solution and to the turbidity whether in tests of thermic accelerated stability or in exposure to light. For the adjustment of the pH and consequently of the osmolarity of the 2-arylpropionic acid salts, mixtures have been used of C_3-C_5 hydroxy di- and tri-carboxylic acids and the alkaline and alkaline earth salts thereof chosen in the group consisting of the tartronic, malic, tartaric and citric acids. Particularly preferred is the use of citric acid combined with the sodium hydroxy and/or sodium citrate.

The dark glass containers are preferably borosilicate phials rendered opaque to light radiations having 290 to 450 nm wave lengths.

Hereunder are given some non-limitative examples of some embodiments of the invention.

Example 1

Working sheltered from light, in an atmosphere and under bubbling nitrogen, 37.5 g (c.a.0.195M) of citric acid and 22.5 g (0.5625M) of sodium hydroxide are dissolved in 12 l of sterile water for injectable preparations, previously de-aerated. To the solution so obtained is added under stirring 1.2 kg (3M) of (R,S)-ketoprofen salt of d,l-lysine controlling the pH of the solution and eventually adjusting it to values varying from 7.0 to 7.5 with additions of sodium hydroxide.

After complete dissolution of the salt, the volume of

the solution is brought to 15 l with sterile water for injectable preparations, previously de-aerated, and stirring is continued for another 15 minutes to ensure the total homogeneity of the solution. Nitrogen is left to bubble on the solution for 15 minutes. Working is kept under pressure and in a nitrogen atmosphere, the solution is filtered through 0.22 micron cartridges, and collected in suitable shielded containers appropriately protected from exposure to the UV light radiations and then run into the machine for filling phials for distribution in 2 ml glass ampoules, which are sealed in a nitrogen atmosphere. After sterilisation, the single phials are placed in containers which are made to hold one or more phials. If desired, the single phial holders can be protected individually by films which make them opaque to the transmission of light.

Example 2

In a similar manner, as described in the preceding Example, working is carried out by substituting the d,l-lysine salt of (R,S)-ketoprofen with the d,l-lysine salt of (R,S)-naproxen which is prepared from 0.2M of d,l-lysine dissolved in 700 ml of water to which is added, heating to the boiling point temperature, 0.202M of finely sub-divided (R,S)-naproxen. From the reaction mixture the salt separates by removing the water for distillation.

Claims

1. A pharmaceutical composition suitable for parenteral administration having anti-inflammatory and analgesic property, characterized by the fact that it contains an alkylammonium salt of a 2-arylpropionic acid selected from the group consisting of ketoprofen, ibuprofen, naproxen, tiaprofenic acid, in racemic as well as in enantiomeric form, in an aqueous solution having an osmolarity between 270 and 310 mOsm/kg and at a pH in the range between 7.0 and 7.5, said solution being free of preservatives and of supporting substances and being prepared and kept in a gas-inert atmosphere.

2. A pharmaceutical composition according to claim 1, characterized by the fact that the inert gas is nitrogen.

3. A pharmaceutical composition according to claim 1, characterized by the fact that the alkylammonium salt of the 2-arylpropionic acid is the d,l-lysine salt of (R,S)-ketoprofen and the inert gas is nitrogen.

4. A pharmaceutical composition according to claim 1, characterized by the fact that the alkylammonium salt of the 2-arylpropionic acid is the l-lysine salt of (R,S)-ketoprofen.

5. A pharmaceutical composition according to claim 1, characterized by the fact that the alkylammonium salt of the 2-arylpropionic acid is the l-lysine salt of R-ketoprofen.

6. A pharmaceutical composition according to claim 1, characterized by the fact that the alkylammonium salt of the 2-arylpropionic acid is the l-dropropizine salt

of R-ketoprofen.

7. A pharmaceutical composition according to claim 1, characterized by the fact that the alkylammonium salt of the 2-arylpropionic acid is the tromethamine salt of S-ketoprofen.

8. A pharmaceutical composition according to claim 1, characterized by the fact that the alkylammonium salt of the 2-arylpropionic acid is the tromethamine salt of R-ketoprofen.

9. A pharmaceutical composition according to claim 1, characterized by the fact that the alkylammonium salt of the 2-arylpropionic acid is the 1-lysine salt of S-ketoprofen.

10. Process for the preparation of the pharmaceutical composition according to claim 1, characterized by that an alkylammonium salt of a 2-arylpropionic acid selected from the group consisting of ketoprofen, ibuprofen, naproxen and tiaprofenic acid is suitably dissolved in water for injectable preparation at a pH between 7.0 and 7.5 in an atmosphere of an inert gas and away from light.

INTERNATIONAL SEARCH REPORT

International Application No PCT/IB 96/01461

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 31/19,A 61 K 31/195,A 61 K 31/38,A 61 K 9/08

According to International Patent Classification (IPC) or to both national classification and IPC6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

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ANHANG ANNEX ANNEXE

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

to the International Search Report to the International Patent Application No.

au rapport de recherche international relatif à la demande de brevet international n°

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INTERNATIONAL SEARCH REPORT

International Application No PCT/IB 96/01461

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 31/19,A 61 K 31/195,A 61 K 31/38,A 61 K 9/08

According to International Patent Classification (IPC) or to both national classification and IPC6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search
20 February 1997

Date of mailing of the international search report
26.03.97

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ANHANG zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX to the International Search Report to the International Patent Application No.

ANNEXE au rapport de recherche international relatif à la demande de brevet international n°

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In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

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